Vaccines Against Respiratory Syncytial Virus: The Time Has Come

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(See the major article by Langley et al on pages 24–33.)

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What is this thing we call immunity?

Does it exist for ills from RSV?

Caroline Breese Hall, 1939–2012

Respiratory syncytial virus (RSV) remains the single most important cause of respiratory tract disease in infants, both in the United States [1] and worldwide [2]. This virus is responsible for bronchiolitis in infants and for clinical disease often indistinguishable from influenza in elderly or immunocompromised hosts. RSV disease was first characterized by astute clinicians such as John Adams in the 1940s, as the cause of primary viral pneumonitis in infants in winter months [3]. RSV was subsequently propagated in Robert Channock’s laboratory in the late 1950s [4], confirming the laboratory and clinical findings of disease caused by “chimpanzee coryza” virus described earlier by Morris et al in 1956 [5]. Over the next 50 years, innovative clinical studies by Caroline Breese Hall, Paul Glezen, Ann Falsey, and many others demonstrated the ubiquity, importance, and potential severity of RSV infection in preterm infants, young children, immunocompromised patients, and elderly individuals [6–8]. The article by Langley et al [9] in this issue of The Journal of Infectious Diseases adds considerably to our knowledge regarding vaccines against RSV, a saga that has been ongoing for decades with remarkably little success [10].

There is still no approved vaccine against RSV. The tragic outcome of a formalin-inactivated, alum-precipitated RSV vaccine candidate in the 1960s has resulted in a near moratorium on RSV vaccine research since that time [11, 12]. The early formalin-inactivated vaccine candidate not only failed to protect young seronegative infants against RSV disease but resulted in severe enhanced respiratory disease in vaccine recipients after wild-type RSV infection during the subsequent season, with 2 deaths in the vaccine arm [13–16]. In the 1990s, prevention of RSV lower respiratory tract disease with administration of polyclonal immunoglobulin [17] and, subsequently, the humanized monoclonal antibody palivizumab [18] directed against the RSV surface fusion (F) protein were landmark developments in terms of both decreasing severe disease in high-risk infants and advancing the field of RSV research. These prevention studies confirmed earlier work demonstrating that maternally derived RSV antibody was, in fact, protective in infants [19]. The studies of RSV prophylaxis set the stage for other innovative strategies to increase antibody titers as a means of protection against RSV disease [20]. These strategies include both active immunization and passive immunization, with maternal immunization as a strategy to provide protective antibody against RSV to the infant, beginning at birth [21, 22]. Recent breakthroughs in the path toward an effective RSV vaccine include the description of the molecular structure and function of the RSV F protein [23, 24], as well as increased acceptance of maternal immunization as a vaccination platform following the 2009 influenza pandemic and recent pertussis epidemics [25, 26]. The unmet clinical need for RSV infection prevention has become globally recognized by researchers, foundations, and the pharmaceutical industry. These factors have accelerated the development of RSV vaccines at an unparalleled rate, and this is good news.

Tracking of new and potential RSV vaccines and monoclonal antibody products by PATH, an international health organization based in Seattle, Washington, has documented the rapid increase in RSV vaccines under development from “less than a handful” in 2004 [27, p 149] to >60 in 2016 [28] (Figure 1). Strategies for these vaccines include passive antibody transfer by maternal immunization of the mother with F-protein vaccines, active immunization of adults and elderly individuals with similar protein vaccines, and active immunization of healthy or at-risk children with live-attenuated vaccines delivered intranasally. The fact that RSV vaccines have the potential for commercial development and widespread clinical use now appears to be well recognized and certainly has the potential to influence the health of children and elderly individuals globally.
The article by Langley et al reports on the first clinical study of a purified recombinant RSV protein F vaccine to preferentially maintain prefusion (preF) conformation in the vaccine form. The preF conformation is the meta-stable form of the RSV F protein prior to attachment to the host cell membrane. The preF conformation has been shown to be the target of the majority of serum neutralizing antibodies to RSV in healthy adults [29]. A vaccine that maintains the preF conformation could theoretically induce a robust neutralizing antibody response directed at the virus prior to attachment to the host cell, thereby mitigating the downstream inflammation that occurs after cell entry. The phase 1 clinical trial in male volunteers was well conducted and powered to assess the immunogenicity and safety of different vaccine doses. Immune responses to a single dose of 10, 30, or 60 µg of preF protein, all with or without alum, were evaluated and shown to induce dose-related antibodies that neutralized both RSV subtypes A and B at the 2 lower doses. Interestingly, antibody responses waned by 6 months and 1 year after immunization. Overall, antibody responses were appropriate, with over half of recipients having a postimmunization neutralizing antibody titer of >1:1024; such levels could theoretically result in antibody titers that might result in protection in adults. This strategy could also be used as part of a maternal immunization strategy to be given early in the third trimester to protect infants through active transplacental transport of maternal antibody.

Figure 1. Snapshot of respiratory syncytial virus (RSV) vaccines under development or under clinical investigation as of 13 July 2016. This figure is provided by PATH, with the assistance of D. Higgins, and can be found at: http://www.path.org/vaccineresources/details.php?id=1562. Abbreviations: CAS, cyclosporine A; LID, Laboratory of Infectious Diseases; mAb, monoclonal antibody; MVA, modified vaccine virus Ankara; NIAID, National Institute of Allergy and Infectious Diseases; NIH, National Institutes of Health; PIV, parainfluenza virus; SeV, Sendai virus; VLP, virus-like particle; VRC, Vaccine Research Center.
are not included in this article and were not publically available at the time this editorial was written. Nonetheless, evaluation of a pref F protein vaccine demonstrating that neither alum nor multiple doses are required is a major advance toward a potential RSV vaccine for pregnant women, as well as other risk groups, such as children with cystic fibrosis or elderly individuals.

This article, in combination with recent notable publications describing the RSV F nanoparticle vaccine, by Glenn et al [30, 31], and the live attenuated RSV ΔM2-2 deleterant mutant in seronegative young children [32] demonstrate the important recent advances in RSV vaccine development. Studies of the F nanoparticle vaccine in 330 women of childbearing age have already demonstrated its safety, dose-response characteristics, and immunogenicity, with increased immunity shown with aluminum phosphate, good safety and immunogenicity with a single-dose vaccine, and potential effectiveness against infection noted in this relatively small study [30]. Two additional clinical trials evaluating this safe and immunogenic vaccine in pregnant women are ongoing, with 50 pregnant women successfully completing the first trial [33] and a second trial of pregnant women now enrolling [34]. Furthermore, the potential of long-acting monoclonal antibodies given directly to very young infants or immunocompromised patients who may be unlikely to mount an appropriate response to vaccination is also under consideration [35].

This increase in approaches to prevention make it imperative that clinicians, public health personnel, laboratories, and medical educators increase their knowledge and awareness of RSV. Data demonstrating the substantial impact of RSV disease in young infants worldwide are accumulating, thanks in part to increased use of sensitive and specific molecular diagnostic tests [36], novel methods of temperature-stable specimen collection and storage [37], and dedicated multicenter epidemiologic studies [38]. RSV vaccines will need to be carefully evaluated in diverse populations, including pregnant women, children, and elderly individuals, with an emphasis on clinical trials in both developed and developing sites, where the epidemiology and disease severity due to RSV may differ substantially. Policies regarding these vaccines will need to be standardized, particularly if vaccines are to be given during pregnancy. With new approaches and new vaccines, novel methods for licensure and measures of standardization of laboratory and clinical end points, both at the national and international level, will be required. New regulatory standards are required for developing vaccines that may be focused as a maternal immunization product, with the Food and Drug Administration (FDA) already addressing this issue publicly [39]. Meetings convened by the National Institutes of Health, FDA, World Health Organization, and others have been and are being held to discuss this issue [40, 41]. Ongoing collaborative work sponsored by the Brighton Collaboration is addressing the standardization of neonatal and maternal definitions applicable to maternal vaccine research [42], and PATH, with the support of the Bill and Melinda Gates Foundation and many investigators worldwide, is working on the standardization of laboratory assays assessing RSV neutralizing antibody, an important surrogate marker for protection against RSV disease. These efforts are providing important consensus criteria for assessing and comparing potential protection in vaccinated subjects.

This is an exciting time for the RSV field. RSV has long been the neglected back-room orphan virus mentioned only as the cause of annual outbreaks of bronchiolitis in infants, but we have new hope that successful collaborations among academicians, clinicians, governmental and international agencies, foundations, regulatory bodies, and the pharmaceutical industry will defeat this important pathogen, which affects both the young and old at all levels of society.

Note
Potential conflict of interest. J. A. E. has been a consultant for Pfizer and a member of the GSK data safety monitoring board for influenza vaccines and received research support for clinical trials from ALios, Gilead, Pfizer, GSK, and Novavax. H. Y. C. certifies no potential conflicts of interest. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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